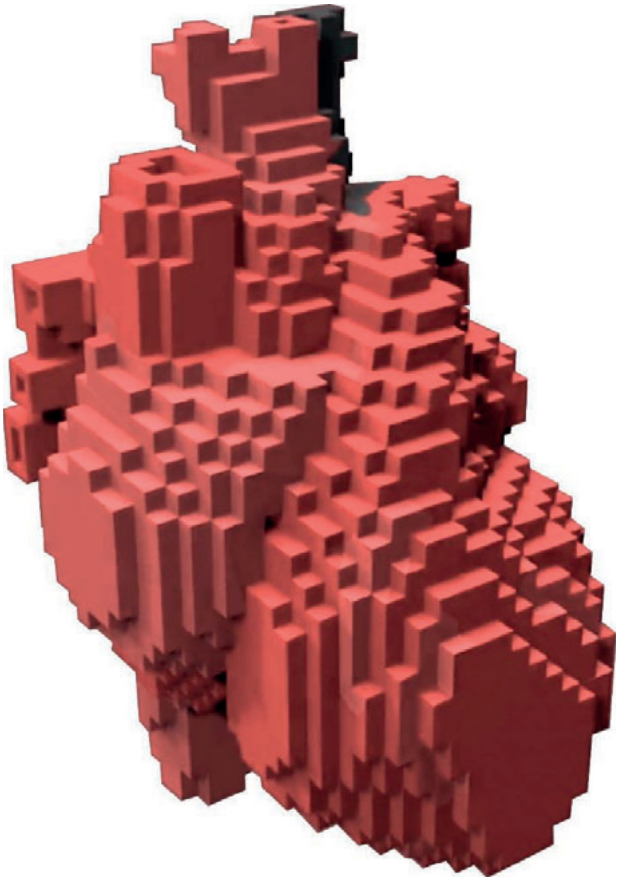
Chapter 6

Summary, general discussion and recommendations



Chemotherapy and radiotherapy for breast cancer may lead to cardiac dysfunction, but the prevalence of long-term echocardiographic evidence of cardiac dysfunction is unknown among long-term survivors. The main objective of this thesis is to determine the prevalence of cardiac dysfunction in an unselected population of long-term survivors of breast cancer, treated with chemo- and/or radiotherapy as compared to matched women without a history of cancer and without chemotherapy for other indications. The prevalence and severity of cardiac dysfunction should be known to determine whether survivors of BC should be more alert to symptoms that might indicate cardiovascular diseases. The same goes for awareness among health care professionals. Furthermore, we aimed to find a subgroup among survivors with a high risk of developing cardiac dysfunction, and we searched for biomarkers that may provide more insight into the aetiology of cardiovascular disease after breast cancer treatment.

This chapter contains the summary of previous chapters, reflections upon methodological considerations, presents reported results into context, discusses clinical implications for research and health care, and presents suggestions for further research and education.

Summary of main findings

Part I

In **part I** of this thesis the results are presented of studies investigating the prevalence of long-term cardiac dysfunction and other cardiovascular diseases in breast cancer survivors from an unselected population and comparing the risks to an age- and general practitioner (GP) matched control group.

In **chapter 2**, the prevalence of cardiovascular disease (CVD) in a retrospective cohort of 561 long-term survivors (≥5 years) of breast cancer was analysed and compared to the prevalence of CVD in 1,635 age- and GP matched controls. In this study, no increased risk of CVD after radiotherapy- and/or chemotherapy was found as compared to controls. Lack of significant findings in this chapter could not necessarily rule out the clinically important risks of CVD related to breast cancer treatment, as the diagnosis of CVD was based on international classification of primary care (ICPC) codes assigned by GPs and not on objective measurements. The hazard ratio (HR) of 1.8 for congestive heart failure after chemotherapy was in line with earlier studies. Because of the uncertainty of coding heart failure some women may have cardiac dysfunction without being diagnosed (as symptoms of heart failure among women with a history of breast cancer may not have been interpreted as such) and/ or patients were diagnosed

with heart failure while that may not have been the case.[188] Furthermore, we could not adjust for risk factors such as smoking, body mass index, family history of CVD, lifestyle, type, and dose of chemotherapeutic agents.

In **chapter 3**, the BLOC study is described. In this large cross-sectional study among 350 women with a history of breast cancer and 350 controls in which all women underwent an echocardiography to measure the cardiac function (systolic and diastolic function). In this study, we found that, both, patients treated with chemotherapy (with or without radiotherapy) and patients treated with radiotherapy-only had a two times increased risk of developing systolic dysfunction as compared to age and GP-matched women without a history of any cancer. Prevalence of systolic dysfunction (defined as LVEF < 54%) was found to be present in 15% of survivors compared to 7% in controls. In addition, more breast cancer survivors were diagnosed with cardiovascular disease and had increased levels of NT-pro BNP. All differences remained significant after adjustment for cardiovascular risk factors. However, systolic dysfunction, in general, was mild and above the clinical threshold for referral or treatment (defined as a LVEF <50% and < 45%, respectively). Bias due to differences in baseline characteristics between the patients and the controls and selective inclusion of controls could not be excluded.

Part II

Early detection of cardiac dysfunction is important as timely treatment might prevent further deterioration of the cardiac function.[119-121] However, monitoring cardiac function through echocardiography is costly and labour intensive, and probably not indicated for the whole group of cancer survivors.[122] **Part II** of the thesis was therefore aimed at gaining more insight into factors associated with a decline in cardiac function on the long-term in breast cancer survivors.

In **chapter 4** a systematic review is presented with an evaluation of the prognostic values of troponin and (NT-pro) BNP in predicting the occurrence of cardiac dysfunction during treatment and follow-up of breast cancer. Of the 691 studies identified, we included 12 studies evaluating 742 patients. The median follow-up of the studies was 0–14 months after the end of breast cancer treatment (range: 0–79 months). Cardiac dysfunction was measured by echocardiography and/or multigated acquisition (MUGA) scan with different cut-off points. The weighted prevalence of cardiac dysfunction at the end of follow-up was 17.8% (range 0%–47%) after a median follow-up ranged 0-12 months. Having an increased troponin level during therapy was not significantly associated with a subsequent occurrence of cardiac dysfunction (OR

3.14; 95%CI 0.73-13.50, I^2 85%). Heterogeneity among studies was high. This heterogeneity could partly be explained by the long follow-up duration of one outlier study, which showed a positive predictive value of troponin. No association was found in the seven studies which evaluated (NT-pro)BNP. Most included studies had a relatively short follow-up, while irreversible cardiac dysfunction due to anthracyclines and radiation may occur more than ten years after treatment. This highlights the need for further studies evaluating predictive factors/biomarkers with a longer follow-up.

In **chapter 5** a study is described that was aimed at exploring whether there were differences in profiles of a set of biomarkers between breast cancer survivors and controls who participated in the BLOC-study. The aim was to identify whether these profiles relate to breast cancer treatment and cardiac function and therewith may aid in identifying patients or give clues to the pathophysiology of cardiotoxicity that may lead to cardiac dysfunction. It showed that women treated for breast cancer with chemotherapy with or without radiotherapy (median 10 years after diagnosis) had significantly higher levels of 24 biomarkers, including inflammatory as well as pro-arteriosclerotic markers compared to women without cancer. After multivariable adjustment for Body Mass Index (BMI), renal function, treatment with radiotherapy and CVD diagnosed at time of cross-sectional measurement, 21 biomarkers were found to be significantly higher in survivors treated with chemotherapy with or without radiotherapy or anti-hormonal therapy compared to controls. This was not found for women treated with radiotherapy-only. Furthermore, several inflammatory biomarkers, elevated in survivors treated with chemotherapy, showed an independent association with lower LVEF

Thesis in context with current literature

Part I

As described in the introduction, previous literature showed an increased hazard of diagnosed heart failure among patients treated with chemotherapy of 1.25 to 1.85 (95% CI 1.07-2.73).[34-37] Results of our retrospective study (HR 1.8; 95% CI 0.6 -5.8) were in line with these results. However, in the cross-sectional BLOC-study (OR 1.0; 95%CI 0.06-16) we did not find an increased risk of a diagnosis of heart failure as registered by GPs among chemotherapy (with or without radiotherapy) treated patients compared to controls. This might be explained by the fact that we could only include breast cancer survivors. Patients that did not survive their breast cancer for at least five years were not included in this study (so-called healthy survivor bias). In our retrospective study we calculated the risks including deceased patients and their causes

of death. No difference was found when risks were compared from those calculated without these patients, except in the group that had received chemotherapy with or without radiotherapy (OR 0.9, 95% CI 0.3–2.9). In the BLOC-study we found, in line with other studies, an increased risk of mild systolic dysfunction (LVEF≤54%; OR 2.5, 95% CI 1.2 – 5.4) and overall diagnosed cardiovascular diseases (OR 2.3; 95%CI 1.0-4.9), which mainly consisted of ischemic cardiovascular disease. Earlier studies attributed ischemic cardiovascular disease primarily to the effects of radiotherapy. As the majority (70%) of patients in the chemotherapy-group in our cross-sectional study was treated with radiotherapy as well, this may have been caused by the combined effect of both therapies. Bias due to differences in baseline characteristics between the patients and the controls and and selective inclusion of controls could not be excluded. Furthermore, differences between earlier studies and our results may be attributed to the usage of lower dose of chemotherapy and the current use of mainly epirubicin instead of doxorubicin, which was the preferred choice in the past.

Among radiotherapy-only treated patients, we did not find increased risks of diagnose cardiovascular disease as registered by GPs in both studies. Though in the cross-sectional study we did find an increased risk of mild systolic dysfunction in these patients compared to controls (OR 2.3; 95%CI 1.1-4.6). A recent meta-analysis including 1,191,371 individuals treated for breast cancer with radiotherapy found an increased risk of coronary artery disease (RR 1.29; 95%CI 1.13-1.48) and cardiac death (RR 1.22; 95% CI 1.08-1.37).[189] However, the treatment era seemed to be associated with the results. The difference with the results of the meta-analysis can be explained by the fact that in the BLOC-study the majority of patients treated with radiotherapy-only were treated with more modern radiation schemes, so that the effects of radiotherapy may be less detrimental to the cardiac muscle. It has been shown that risk of ischemic cardiac disease is linearly correlated with the cardiac dose.[46, 190] The reduction of the cardiac dose in current schemes decreases the risks associated with it and may become even less in the future with for instance breath holding techniques.

Lastly, a high prevalence of diastolic dysfunction was found among both survivors and controls.

Part II

NT-proBNP and troponin are used in clinical practice as important diagnostic markers for acute cardiac pathology.[124, 191-193] Experimental research has shown that exposure to anthracycline chemotherapy causes a dose-dependent reduction in cardiomyocyte contractility that correlates with the release of the cardiac-specific biomarker troponin T.[126] Furthermore, several studies have found that NT-proBNP and BNP are negatively correlated with the left ventricular ejection fraction (LVEF) in patients receiving cardiotoxic treatments for breast cancer.[127-131] These markers are therefore used as diagnostic marker in detecting acute cardiac dysfunction during treatment. Both markers have been suggested as potential prognostic markers as well. Troponin may predict mortality in patients with chronic kidney[194] or established heart failure.[195] NT-proBNP may predict mortality in patients with chronic obstructive pulmonary disease[196] or acute coronary syndrome.[197] The systematic review showed that there is insufficient evidence to date that either troponin or (NT-pro)BNP predict the development of cardiac dysfunction during treatment or follow-up. This may be caused by the relatively short follow-up of included studies and small sample size in the majority of the studies. Further studies are needed to assess the prognostic value of these biomarkers.

Earlier research has suggested that chronic inflammation is associated with cancer, CVD and depression. Furthermore, increased BMI and waist circumference are associated with higher levels of biomarkers related to inflammation.[198-200] Our explorative biomarker analysis showed that breast cancer survivors treated with chemotherapy or anti-hormonal drugs more often showed higher levels of biomarkers related to chronic inflammation than controls. However, these increased levels may also be due to other causes besides anti-cancer therapy, For example, the prevalence of depression may have been increased among chemotherapy-treated patients.[201] And, cancer recurrences are found more often after chemotherapy-including treatment as compared to radiotherapy-only treatments, as tumours treated with chemotherapy are more invasive and tend to have more lymph node involvement.[202] Concerning women treated with anti-hormonal drugs, the protective effects of oestrogens for cardiovascular disease may be lost as aromatase-inhibitors reduce their concentration.[182, 183]

Methodological considerations

Methodological choices in design and dealing with risk of bias may influence the outcome of a study. In this thesis we performed two cohort studies, one retrospective analysis of an already existing cohort and one cross-sectional cohort study. In both studies, women treated for breast cancer with chemo and/or radiotherapy were compared to women without a history of any cancer and without chemotherapy for other indications. The outcomes were cardiovascular disease and cardiac dysfunction. It is important to keep the following methodological considerations in mind when interpreting the results of our studies.

First of all it is important to have a representative sample of the population.[203] As described earlier, most long-term studies on cardiotoxicity of chemotherapy followed patients who participated in randomized controlled trials with strict inclusion and exclusion criteria. This limits the generalizability of the results of these studies.[204] For that reason, we have set up a study including women from the general population. In addition, we included women from a large number of GPs, instead of performing a single center study.

In the cross-sectional study, the participating rate in breast cancer survivors was high (70%), allowing for an accurate risk assessment for cardiac dysfunction. However, the participation rate in women without a history of cancer was lower compared to that of women with breast cancer (48%). In addition, from GP files we learned that non-participating eligible controls had a higher prevalence of diagnosed ischemic diseases than those that did participate. This may have caused an underestimation of the risks among controls and thus an overestimation of the relative risk of ischemic disease of breast cancer survivors. Furthermore, though retrospective or cross-sectional studies are time efficient, they are limited by the fact that information about deceased patients is not available. In the retrospective analysis we were able to analyze a subset of the cohort for which the data on cause and time of death were known from 1998 onwards. Risks calculated including deceased patients and their causes of death did not differ from those calculated without these patients, except for the risk of congestive heart failure in the group that had received chemotherapy (which was lower). This finding may be explained by the fact that chemotherapy-treated patients develop heart failure earlier in life as compared to their controls and they may therefore die of it earlier as well. The effect on our results could be that we missed a difference in risk of congestive heart failure between chemotherapy treated women and controls in the younger aged women. In the elderly

women we expect that the difference in risk diminish because of the dominant effect of age on the risk of congestive heart failure.

Secondly, when analyzing cardiovascular dysfunction/disease prevalence, it is important to consider confounding variables. An important risk factor for cardiovascular disease in high-income countries such as the Netherlands is the socio-economic status (SES).[205] To minimize the differences in SES between breast cancer survivors and women without a history of breast cancer, participants in our studies were matched on their GP. In the Netherlands GPs are grouped in certain postal areas with similar social-economic status among their patients. Furthermore, women were matched on age.

A strength of this study was that risk factors for cardiovascular disease, such as diabetes and hypertension, were extracted from the files of the GPs, instead of using self-reported data. Diagnosis of cardiovascular disease and related risk factors were recorded by participating GPs using the International Classification of Primary Care (ICPC).[85] As breast cancer survivors and women without a history of cancer are both derived from the same general practice, coding is considered similar between both groups. Furthermore, as data is gathered prospectively and embedded in daily care by GPs, we have a low number of missing data.

Implications for practice and research

Understanding the long-term cardiovascular risks associated with chemo- and/or radiotherapy for breast cancer is important when discussing the consequences of cardiac dysfunction, for awareness among physicians, guidelines development and advice for a healthy life style.

Consequences of cardiac dysfunction

In this thesis, breast cancer survivors were shown to have a two times increased risk of systolic dysfunction and cardiovascular disease. However, the majority of women with systolic dysfunction in this study had a left ventricular ejection fraction (LVEF) between 54 and 50%, which is considered a mild dysfunction. There is little association between the level of LVEF and clinical symptoms. Having mild systolic dysfunction alone has no clinical consequences with regard to referring to cardiologists or starting medical interventions. However, it may be considered as stage B heart failure.[206] Stage B, as defined by the American Heart Association (AHA) guidelines, comprises of patients with structural heart disease without current or prior symptoms.[207] Studies have shown that left ventricular (LV) dysfunction is associated with an increased risk of developing

congestive heart failure as compared to individuals without LV dysfunction (hazard ratio of 4.7 [95%CI 2.7-8.1]), adjusted for other risk factors (e.g. age, sex, myocardial infarction, systolic blood pressure, antihypertensive medication use, diabetes, smoking).[208] Congestive heart failure leads to a significant decreased quality of life of patients.[209] Although the benefit of treating patients with symptomatic heart failure has been investigated, data on the treatment of LV dysfunction without symptoms or with a LVEF above 45% is scarce.[206, 210, 211] Estimates of the benefit effect of treatment vary between no treatment effects to a 43% reduction in relative mortality risk.[206, 212-214] The American guidelines recommend to start treatment with an ACE-inhibitor in case of mild systolic dysfunction and to treat cardiac risk factors rigorously.[215] On the contrary, European guidelines are more conservative and do not follow these recommendations.[103]

Women with advanced cardiomyopathy due to treatment with chemo- and/or radiotherapy for breast cancer have similar benefits of treatment as compared to patients with advanced cardiomyopathy due to other causes.[41] Randomized controlled trials examining whether early treatment in patients with LV dysfunction due to chemo- and radiotherapy is beneficial on the long-term, are lacking. A recent meta-analysis on short-term effects showed promising results. In this study, adult cancer patients treated with β-blockers and/or angiotensin antagonists during cardiotoxic treatment had a significantly higher LVEF (mean difference 6.06%; 95%CI 0.74-11.58; I^2 96%) after 6-12 months of treatment compared to those not treated with these drugs. [216]

Furthermore, though the risk of diastolic dysfunction of women treated with chemo- and/or radiotherapy for breast cancer was not significantly increased compared to controls in our cross-sectional study, a high prevalence of diastolic dysfunction was found among both survivors and controls. Diastolic dysfunction is associated with an increased mortality.[53] No specific treatment for diastolic dysfunction/heart failure is available. Therefore, management is aimed at treating risk factors, such as hypertension, hyperlipidaemia and metabolic syndrome.[217]

Awareness among physicians

Creating awareness among physicians is an important step in the cardiac follow-up of women treated with chemo- and/or radiotherapy for breast cancer. For GPs it is important to be aware of the possible long-term cardiotoxic effect, as they are care providers on the long-term after breast cancer treatment. In the Netherlands GPs act as gatekeepers for referrals to medical specialists in the hospital.[84] So, long-term survivors of breast cancer with possible cardiac dysfunction are first assessed by their

GPs. However, it has been shown that recognition of cardiac symptoms is more difficult in women compared to men.[39] Cardiac dysfunction is often not diagnosed in women because symptoms can gradually develop and symptoms are vague[218, 219] such as fatigue and hot flushes. These symptoms are already highly prevalent among breast cancer survivors.[220-222] Being more aware of the prevalence may aid in diagnosing cardiac dysfunction early (case-finding). Furthermore, also for medical specialists it is important to be aware of the long-term cardiotoxicity associated with breast cancer treatment. For instance, anaesthesiologists should be aware that the physiological reserve may be significantly impaired (despite a normal appearance), which might become apparent in the peri-operative period when the patient is physiologically stressed.[223] Furthermore, it has been shown that anthracyclines-treated patients under anaesthesia can develop acute intra-operative LV failure refractory to β-adrenergic receptor agonists.[223] One of the ways to create awareness among physicians is to incorporate information regarding possible risks in education.

Routine cardiac follow-up and cardiovascular risk assessment

Since early detection of cardiac dysfunction can be difficult, some might think that promoting physicians' awareness is too limited to prevent deterioration of the cardiac reserve. For them, the possibility remains to treat cardiovascular risk factors (such as hypertension and dyslipidaemia) rigorously as described in the AHA guidelines.[206, 207] In the Netherlands, GPs are well equipped and trained to handle cardiovascular risks.[71, 84, 224] Furthermore, they are trained and equipped to treat cardiovascular risk factors. As described in the general introduction, chemo- and/or radiotherapy may have a direct effect by damaging the cardiomyocytes, and a possible indirect effect described by the multiple-hit theory.[69, 70] These additional hits may be prevented by treating cardiovascular risk factors rigorously and by pursuing patients to maintain a healthy lifestyle. The Dutch cardiovascular risk management guideline (CVRM 2013) is aimed at doing this.[71] Based on several risk factors, a risk estimate is made of the absolute 10 years risk of morbidity or mortality due to cardiovascular disease. Based upon this risk, the need for further treatment is assessed. Risk factors taken into account when identifying patients with an increased risk eligible for cardiac risk assessment are: prior diagnosis of cardiovascular disease, diabetes, and rheumatoid arthritis. In addition patients with a systolic blood pressure of >140 mmHg, total cholesterol >6.5 mmol/l, smokers ≥ 50 yrs., patients with first degree family members with cardiovascular disease before the age of 65, and patients with chronic kidney disease need to be offered a cardiac risk assessment according to current guidelines.[71]

Risk estimates by the CVRM (2013) are adjusted for patients with prior cardiovascular disease (based on type), diabetes (15 years added to age), or rheumatoid arthritis (2 times increased). The increased risk in case of rheumatoid arthritis is possibly due to the inflammatory nature, which induced chronic inflammation in the vessel wall with similar effect on the vessel wall as in atherosclerosis. Based upon this the European League Against Rheumatism proposed that the estimate for the ten year risk of CVD in patients with rheumatoid arthritis had to be increased with a factor 1.5 according to the current Dutch cardiovascular risk factor guideline. As for now there is insufficient evidence that the estimated ten year cardiovascular risk should be increased in survivors of breast cancer. As shown in chapter 5 of this thesis, a breast cancer patient treated with chemotherapy and/or anti-hormonal treatment also has an increased level of biomarkers related to inflammation as compared to controls, even in the absence of cardiovascular disease. Further research should show whether breast cancer treatment or one of these biomarkers might be relevant factors to include in the CVD risk assessment.

Healthy lifestyle during and after (breast) cancer treatment

As mentioned in the introduction, an unhealthy lifestyle has been associated with an increased risk of cardiovascular disease and breast cancer. Modifiable lifestyle factors include smoking, physical inactivity, an unhealthy diet, and high alcohol consumption. A recent meta-analysis showed that adherence to a healthy lifestyle reduces the risk of cardiovascular disease by 66% (HR 0.34, 95%CI 0.28 – 0.48, I^2 79.1%), with similar results in women and men. [225] In addition to decreasing the risk of cardiovascular disease, a healthy lifestyle may also decrease the risk of breast cancer recurrences. [226]

Although we have assessed BMI, smoking habits and physical activity as variables, we have not performed any specific analyses related to the influence of these factors so far. However, it is important to pay attention to these risk factors when discussing the effect of breast cancer therapy and cardiac dysfunction. Studies have shown that up to 70% of cancer survivors do not adopt to a healthy lifestyle in the US and Australia.[227-229] This is possibly due to the high prevalence of fatigue and (symptoms of) depression after cancer therapy.[201, 230] However, it has been shown that breast cancer patients, who are involved in physical activity during active chemotherapy treatment, experience increased well-being and restored energy levels.[231] In our study no differences were seen in BMI and physical activity levels among our cohorts in the BLOC study. Nevertheless, 57% of the breast cancer survivors had a BMI > 25kg/m2, 25% were physical inactive, and 19% were still active smokers at time of assessment.

There may indeed be a considerable potential to decrease CV disease and breast cancer recurrence risk in this area.

One way to accomplish a healthier lifestyle is to create awareness among patients. Women have been shown to pursue a healthier lifestyle when they perceive themselves to be at risk and know the goals of prevention.[232] Furthermore, it has been shown, that women in general are inclined to wait longer before seeking medical attention with symptoms of cardiac disease compared to men.[40] Knowing their risk can help maintain a healthier lifestyle and call for medical attention more quickly. Creating awareness and providing aid as to when to seek medical attention, may be done by a tool such as Oncokompas, which gives a personalized recommendation based upon a questionnaire.[233]

Suggestions for further research

As described above it is probably not useful to screen all breast cancer survivors for cardiac dysfunction. However, identifying a high-risk group among breast cancer survivors treated with chemo- and/or radiotherapy may be beneficial.

Several factors have been investigated to identify a high-risk group. As shown in chapter 4, there is insufficient evidence to date that troponin or (NT-pro)BNP predict the development of cardiac dysfunction during treatment or follow-up. However, the follow-up period of included studies was short and the majority consisted of a small sample size. Since irreversible dysfunction occurs more than five years after treatment, there is a need for studies with a longer follow-up that determine the prognostic value of biomarkers measured during treatment. In addition to troponin and (NT-pro)BNP, strain measurement have also been mentioned as a tool to identify patients with early damage.[62, 234] However, this is a time-consuming method. Furthermore, steps have been taken to identify early high-risk groups in breast cancer patients by analysing the radiation schemes and heart dose.[46, 190] Furthermore, it might be possible to identify a genetic profile which determines which women are highly susceptible to develop cardiac dysfunction after chemo- and/or radiotherapy.[158] Detection of patients with a specific genetic profile may lead to specific monitoring and a more personalized oncologic therapy aimed at reducing cardiotoxicity.[235] All mentioned methods of identification may be included in a clinical predictive model at the end of treatment to make an accurate risk assessment in the group of breast cancer survivors who have been treated with chemo- and/or radiotherapy. Research showed that the power of current risk scores is limited with areas under the curve of about 0.70.[158]

The usefulness of detection of cardiac dysfunction at an early stage depends on the possibility to reduce further deterioration. Following patients in the BLOC cohort over the years could indicate whether the mild cardiac dysfunction ultimately leads to more severe cardiac impairment compared to controls. Furthermore, three groups of cardiovascular medication have been proposed to have cardio protective effects during or after treatment: β-blockers, ACE inhibitors, and statins.[54, 236] Whether these medications prove to have a cardioprotective effect on the long-term still remains to be determined. Additionally, as our explorative biomarker analysis showed, chemotherapy-treated or anti-hormonal treated breast cancer survivors showed a distinct pro-inflammatory and pro-arteriosclerotic biomarker profile. Targeting these pathways may be a promising strategy in treating and preventing cardiac dysfunction among survivors.[186, 187, 237]

Overall Conclusion

In this thesis, we have shown that long-term breast cancer survivors treated with chemo- and/or radiotherapy have a twice as high risk of developing mild systolic cardiac dysfunction and cardiovascular diseases compared to controls in a general practice population. Furthermore, we have shown that long-term breast cancer patients treated with chemotherapy or anti-hormonal drugs have on average a higher pro-inflammatory and pro-arteriosclerotic biomarker profile then controls. This may be a clue to finding treatment options or to the selection of a subgroup of patients at high risk for cardiac dysfunction or cardiovascular diseases.

These results suggest that cardiovascular risk prevention does not has to be adjusted for survivors of breast cancer. Because 15% of women treated for breast cancer with chemotherapy (with or without radiotherapy) have a reduced cardiac reserve, it is important for these women to maintain a healthy lifestyle and monitor their cardiac risk factors. Future studies may identify a high-risk group in these patients, examine whether treatment of cardiovascular disease may be useful, for example by anti-inflammatory drugs, and may show whether the mild cardiac dysfunction among breast cancer survivors ultimately leads to more severe cardiac impairment compared to controls. It is important to keep in mind that the cardiotoxicity of oncological treatment for breast cancer is decreasing over time due to improvements of techniques and the limitation of chemotherapy dosage. A massive decline in current rate is not expected, but heart failure rates as seen in the early days are no longer common.